



## Full length article

A hypothetical aging pathway from skin to hypothalamic suprachiasmatic nucleus via slow wave sleep<sup>☆</sup>

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## ABSTRACT

Many observations have demonstrated that the hypothalamic neuroendocrine change determines the chronological sequence of aging in mammals. However, it remains uncertain on the mechanism to account for the hypothalamic aging manifestations. In this article, it is pointed out that, as constantly exposed to sunshine and oxygen, the skin would undergo both telomere-shortening and oxidative senescent processes. The senescent alterations of skin, such as attenuation in electrodermal activities, would in turn reduce the emotional responses and memories. Whereas previously I demonstrated that the slow wave sleep just functioned to adjust the emotional balance disrupted by accumulated emotional memories, especially capable of ameliorating the symptoms of depressed patients. Therefore, the reduction in emotional responses and memories from skin senescence would reduce the requirement for slow wave sleep in many senescent observations. The decrement in slow wave sleep would in further cause functional but not chronological degeneration of suprachiasmatic nucleus rather than paraventricular nucleus in hypothalamus. In these respects, from skin senescence to slow wave sleep, there forms a new degenerative aging pathway able to account for the hypothalamic chronological sequence of aging, specifically addressed to the suprachiasmatic nucleus.

## 1. Introduction

Mammalian aging is a complex degenerative process involving many biochemical, cellular and physiological changes. The underlying mechanisms for mammalian aging have been diverse, and remained controversial on which plays more important roles than others. Among the mechanisms, there are oxidative accumulations in cells [1–4], length-shortening of telomeres [5,6], chronological changes in hypothalamic neuroendocrine control of hormones [7,8], thymic involution [9,10], amyloid-beta accumulation in brain [11,12], and so on.

In spite of the various aging mechanisms, the hypothalamic neuroendocrine change determines the chronological sequence of aging in mammals. Whereas, it remains uncertain on the mechanism to explain the hypothalamic chronological manifestation of aging. On the other hand, not all aging processes are controlled by the hypothalamic neuroendocrine system in mammals. Aging processes such as thymic involution [9,10], brain senescence [11,12], as well as skin exposure to sunshine and oxygen are all beyond the influence of hypothalamic neuroendocrine control. In this theoretical essay, it is attempted to hypothesize a mechanism to account for the hypothalamic aging of suprachiasmatic nucleus (SCN) with skin senescence beyond the hypothalamic neuroendocrine control.

## 2. Integrative review as the method to raise new hypothesis

This paper belongs to a theoretical essay. Many theoretical essays are adopted in the form of review, so is this paper. To raise a new hypothesis, there is no better and more convincing way than integrative reviewing all relevant fields of studies. It is necessary to point out that meta-analysis fits hypothesis in a well-studied subfield, but not for integrative hypothesis from several fields. Citing updated reviews or, if not available, salient and repeated experimental results in subfields is the best method. With this integrative methodology, in this paper, it is hypothesized a new theory on the mechanism for the hypothalamic aging of SCN with skin senescence.

## 3. The vulnerability of skin to aging

Since thymic involution [9,10], brain senescence [11,12] as well as skin aging from sunshine and oxygen are all beyond the hypothalamic control, it is necessary to briefly review them for the purpose of finding out the plausible candidate of mechanism responsible for causing hypothalamic aging.

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### 3.1. Thymic involution

Thymic involution occurs early in childhood before puberty [9,13], which is dissociated from the later aging processes controlled by the hypothalamic neuroendocrine system. Thymic involution is believed to contribute to morbidity and mortality in elderly humans due to the increased incidence of infection, autoimmunity, and cancer [10,13]. Whereas, the later aging processes controlled by hypothalamic neuroendocrine system manifest mainly as decrease in sexuality [14] and increase in stress [8]. In this regard, the aging processes of thymic involution and hypothalamic neuroendocrine dysfunction are dissociated but concurrent with each other.

### 3.2. Amyloid-beta and brain aging

The hypothalamus is in turn controlled by many higher brain structures, so that the brain aging, characterized as the accumulation of amyloid-beta [4,11], is also beyond the hypothalamic neuroendocrine control. In reverse, the hypothalamic aging may result from brain aging. However, recently it was reported that sleep helped biophysical clearance of amyloid beta from the adult brain [12,15], implicating that the neurons of brain were equally subject to the aging toxicity of amyloid beta, including the hypothalamic nuclei.

Investigation on hypothalamic change during aging revealed that each cell group of the hypothalamic nuclei had their own specific pattern of aging, some decreasing while others increasing in volume during aging [7,16–18]. Since the biophysical homogeneity in toxicity of amyloid beta from forebrain [12,15] would cause homogenous degeneration of all hypothalamic nuclei, the heterogeneity in degeneration of hypothalamic nuclei [7,16–18] indicated that the hypothalamic aging would result from the aging mechanisms other than the toxicity of amyloid beta from forebrain.

### 3.3. Sunshine, oxygen, telomere length and skin aging

After exclusion of thymic involution and forebrain amyloid-beta as the cause of hypothalamic aging, skin aging is the major process not controlled by the hypothalamic neuroendocrine system, and most likely to feedback to cause hypothalamic aging.

Skin aging is characterized in appearance as gray in hairs, increase in wrinkles, deposition of pigments and so on. Skin is constantly exposed to sunshine and oxygen, which makes skin aging beyond the influence from hypothalamic neuroendocrine system. It has been demonstrated that dysfunction of skin collagen [19] and elastin [20] may be responsible for the generation of skin wrinkles from photoaging. It has also been demonstrated that oxidative accumulations are intimately associated with skin aging [21,22]. Obviously, both sunshine and oxygen are the environmental causes resulting in the aging of skin.

In addition to the damage from environmental sunshine and oxygen, the skin also undergoes aging genetically by shortening the length of telomeres. It has been shown that the telomerase activity and telomere length may be relevant to skin aging [23]. Particularly, it was reported that the telomerase reversed the hair follicle stem cell defects in epidermis [24]. Obviously, genetic shortening telomere length is an additional mechanism causing skin aging in addition to environmental sunshine and oxygen.

### 3.4. Skin aging and electrodermal activities

One of the important consequences of skin aging is the change in electrodermal activities. It was reported that the electrodermal activities decreased in the older subjects than younger [25,26]. At the cellular level, it was shown that the electrodermal activity was intimately related to the count and filling of sweat glands [27,28]. Likewise, it was demonstrated that the sweating response was decreased during aging in humans [29,30]. In this regard, both electro-

dermal activities and sweating responses were reduced in parallel during aging.

## 4. Aging, emotion and slow wave sleep

### 4.1. Electrodermal activities in depression and aging

Emotional response can also cause changes in electrodermal activities. It has been demonstrated that the psychological stress can elicit significant changes in electrodermal activities in humans [31,32]. Whereas, it has also been shown that the electrodermal activities vary among subgroups of depressive patients [33,34], with a tendency of decrease in electrodermal activity during acute suicidal period [35].

As has been demonstrated above, in aging the electrodermal activities were reduced [25,26]. In this regard, aging parallels to depressive patients with suicidal tendency as reduction in electrodermal activities.

It is common knowledge that both aging [7,8] and depression [36–38] result from long-term accumulation of stress. In this regard, the parallel of aging and depression on electrodermal activity is consistent with the fact that they both result from stress.

On the other hand, as has been demonstrated above, decrease in electrodermal activities during aging results from the environmental sunshine and oxygen as well as the genetic shortening of telomere length. In this regard, it is the skin damage and aging that reduces the electrodermal activities in similarity to depression, manifesting the shift of body state toward depression.

### 4.2. Slow wave sleep ameliorating depression from emotional memories

Previously, through integrative review of various studies, I demonstrated that slow-wave sleep (SWS) played the function in regulation of emotional balance disrupted by emotional memories randomly accumulated during waking [36–38], while the rapid-eye-movement (REM) sleep played the opposite role [36–38]. This theoretical analysis on sleep functions pertains to Freudian psychoanalysis more than other sleep theories [38].

In this theoretical analysis on sleep functions, there reviewed the observations and experiments in many aspects [36–38]. For the emotional regulation of SWS, there were integratively reviewed [36–38] as: (1) SWS was frequently related with depression, while increase in SWS duration ameliorated depression [36–38]. (2) Hippocampal but not neocortical lesions caused impairment of SWS, while the neuronal activity in SWS increased in hippocampus but not in neocortex [36–38]. For the REM sleep, I and others reviewed it as tending to disrupt the emotional balance toward depression [36–40], with the REM sleep deprivation cited as therapeutic against depression [36–38].

The function of REM sleep matches to the Freudianism that learned memories conflict against disinhibited drives during dream sleep, consolidating the psychoanalysis of Freudianism [38]. Whereas, the function of SWS in contrary to that of REM sleep supplements the neglect of Freudianism, important to further advancement of psychoanalytic theory and therapy in future.

### 4.3. Aging, emotional memory and slow wave sleep

Aging [25,26] and depression with suicidal tendency [35] both manifest reduction in electrodermal activities, indicating decrease in physiological responses of emotion [31,32]. In this regard, emotional memories would also be reduced in accordance.

SWS just plays the function in regulation of emotional balance disrupted by emotional memories randomly accumulated during waking [36–38]. Decrease in emotional memories would result in decrease in requirement for SWS to adjust their disrupted emotional balance. In this regard, SWS would decrease in duration during aging. Indeed,

many observations have demonstrated that SWS really decreases in duration during aging [41–43].

## 5. Slow wave sleep and aging of suprachiasmatic nucleus in hypothalamus

### 5.1. Heterogeneity of hypothalamic nuclei in aging

The hypothalamic nuclei manifest variation in degeneration during aging [7,16–18]. The paraventricular nucleus (PVN) is responsible for stress response and is functional throughout the lifespan, maintaining its neuron number during aging [7,16]. In contrast, the number of vasoactive intestinal polypeptide (VIP) neurons is decreased in the SCN as the main controller of circadian rhythm during the process of senescence [7,16–18], consistent with the gradual decrease in SWS during aging [41–43]. Moreover, the sexually dimorphic nucleus in preoptic area (SDN-POA) declines sharply in cell number after aging [7,16]. This nucleus is twice as large in men as in women [7], manifesting its functional differentiation in sex. In all, the hypothalamic nuclei manifest differentiation in degeneration corresponding to their functions in aging, with useful maintained while useless degenerated.

### 5.2. Slow wave sleep and aging of hypothalamic suprachiasmatic nucleus

As mentioned above, in response to skin aging and reduction in emotional memories, the SWS is observed to decrease gradually in duration during aging [41–43]. The SCN controls the circadian rhythm, while the reduction in SWS would reduce the requirement for the function of SCN. In this regard, the hypothalamic SCN follows to degenerate during aging [7,16–18], as other neurons and muscles. In turn, many biological processes controlled by hypothalamic SCN also become less coordinated during aging. In this regard, herein it is formulated a hypothalamic aging pathway from skin senescence to degeneration of hypothalamic SCN in aging via SWS.

The aging-related disorganization in expression of core clock genes in various brain regions supports this hypothetic pathway. It is common knowledge that the hippocampus is responsible for learning and memory [44]. It was demonstrated that the expression of *Clock*, *Bmal1* and *Per2* genes in hippocampus lost circadian rhythm earlier than those in hypothalamic SCN [45,46], implicating that the hippocampal circadian rhythm relevant to SWS for adjusting the memories therein decreased earlier in response to reduction of emotional responses, while such dysfunctions later began to affect the hypothalamic SCN.

## 6. Perspectives

The new theory for the aging pathway from skin to hypothalamic SCN via SWS is significant. On the one hand, it provides an explanation to account for the chronological aging of hypothalamic SCN with the cellular senescent processes from skin via SWS, arguing against the conceivable cause of aging chronologically set by the intrinsic circadian rhythm within the SCN. In consistence, the expression of *Clock*, *Bmal1* and *Per2* genes in hippocampus lost circadian rhythm earlier than those in hypothalamic SCN [45,46]. In parallel, this mechanism also provides a clue to understand how other hypothalamic nuclei undergo degeneration during aging in similarity. On July 4, 2016, the European people in television speculated that there was a similar senescent pathway for male reproduction from accumulation of lipid to reduction of sperm to degeneration of hypothalamic preoptic area, while senescence of female reproduction likely resulting from ovary degeneration.

On the other hand, it provides a useful theory to guide the therapeutic efforts against aging in future. With regard to SCN degeneration during aging, the therapeutic anti-aging efforts should

be more devoted to skin protection, sleep recovery and so on. In these regards, this new theory would be important to biomedical sciences.

## 7. Conclusions

In this article, it is pointed out that the skin undergoes aging from exposure to environmental sunshine and oxygen as well as genetic shortening of telomere. The skin senescence results in reduction in electrodermal activities, which would in turn ameliorate the emotional responses and memories in brain, and thus reduce the requirement for SWS. The decrement in duration of SWS in many senescent observations would in further cause functional but not chronological degeneration of SCN in hypothalamus during aging. In this regard, from skin senescence to SWS, it is herein formulated a new degenerative aging pathway to explain the hypothalamic chronological sequence of aging addressing to SCN.

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